

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GRALISE safely and effectively. See full prescribing information for GRALISE.

GRALISE® (gabapentin) tablets

Initial U.S. Approval: 1993

### INDICATIONS AND USAGE

GRALISE is indicated for the management of Postherpetic Neuralgia (PHN).

**Important Limitation: GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration** (See Warnings and Precautions)

### DOSAGE AND ADMINISTRATION

- GRALISE should be titrated to an 1800 mg dose taken orally, once-daily, with the evening meal. GRALISE tablets should be swallowed whole. Do not crush, split, or chew the tablets. (2.1)
- If GRALISE dose is reduced, discontinued, or substituted with an alternative medication, this should be done gradually over a minimum of 1 week or longer (at the discretion of the prescriber). (2.1)
- Renal impairment: Dose should be adjusted in patients with reduced renal function. GRALISE should not be used in patients with CrCl less than 30 or in patients on hemodialysis. (2.2)

### DOSAGE FORMS AND STRENGTHS

- 300 and 600 mg tablets (3)

### CONTRAINDICATIONS

GRALISE is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. (4)

### WARNINGS AND PRECAUTIONS

- GRALISE is not interchangeable with other gabapentin products
- Antiepileptic drugs, including gabapentin, the active ingredient in GRALISE, increase the risk of suicidal thoughts or behavior (5.1)
- Increased seizure frequency may occur in patients with seizure disorders if GRALISE is rapidly discontinued. Withdraw GRALISE gradually over a minimum of 1 week. (5.2)

### ADVERSE REACTIONS

The most common adverse reaction (greater than or equal to 5% and twice placebo) is dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Depomed, Inc. at 1-866-458-6389 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### DRUG INTERACTIONS

- An increase in gabapentin AUC values have been reported when administered with hydrocodone. (7.6)
- An increase in gabapentin AUC values have been reported when administered with morphine. (7.7)
- An antacid containing aluminum hydroxide and magnesium hydroxide reduced the bioavailability of gabapentin immediate release by about approximately 20%, but by only 5% when gabapentin was taken 2 hours after antacids. It is recommended that GRALISE be taken at least 2 hours following antacid administration. (7.10)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: GRALISE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- Nursing Mothers: GRALISE should be used in women who are nursing only if the benefits clearly outweigh the risks. (8.3)
- Elderly: Reductions in GRALISE dose should be made in patients with age-related compromised renal function. (8.5)
- Renal impairment: Dosage adjustment is necessary for patients with impaired renal function. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2012

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Postherpetic Neuralgia
- 2.2 Patients with Renal Impairment

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Suicidal Behavior and Ideation
- 5.2 Withdrawal of Gabapentin
- 5.3 Tumorigenic Potential
- 5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity
- 5.5 Laboratory Tests

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing and Other Experience with other Formulations of Gabapentin

### 7 DRUG INTERACTIONS

- 7.1 Phenytoin
- 7.2 Carbamazepine
- 7.3 Valproic Acid
- 7.4 Phenobarbital
- 7.5 Naproxen
- 7.6 Hydrocodone
- 7.7 Morphine
- 7.8 Cimetidine
- 7.9 Oral Contraceptives
- 7.10 Antacid (containing aluminum hydroxide and magnesium hydroxide)
- 7.11 Probenecid
- 7.12 Drug/Laboratory Test Interactions

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

### 9 DRUG ABUSE AND DEPENDENCE

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Special Populations

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

- 17.1 Medication Guide
- 17.2 Suicidal Thoughts and Behavior
- 17.3 Dosing and Administration

\*Sections or subsections omitted from the full prescribing information are not listed

1 **FULL PRESCRIBING INFORMATION**

2 GRA-004-C.5 SEP 2012

3 GRALISE® (gabapentin) Tablets

R<sub>x</sub> only

4 **1 INDICATIONS AND USAGE**

5 GRALISE is indicated for the management of postherpetic neuralgia.

6 GRALISE is not interchangeable with other gabapentin products because of differing  
7 pharmacokinetic profiles that affect the frequency of administration.

8 **2 DOSAGE AND ADMINISTRATION**

9 **2.1 Postherpetic Neuralgia**

10 Do not use GRALISE interchangeably with other gabapentin products.

11 Titrate GRALISE to an 1800 mg dose taken orally once daily with the evening meal.  
12 GRALISE tablets should be swallowed whole. Do not split, crush, or chew the tablets.

13 If GRALISE dose is reduced, discontinued, or substituted with an alternative medication,  
14 this should be done gradually over a minimum of one week or longer (at the discretion of the  
15 prescriber).

16 In adults with postherpetic neuralgia, GRALISE therapy should be initiated and titrated  
17 as follows:

18 **Table 1: GRALISE Recommended Titration Schedule**

	<b>Day 1</b>	<b>Day 2</b>	<b>Days 3–6</b>	<b>Days 7–10</b>	<b>Days 11–14</b>	<b>Day 15</b>
Daily Dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

19  
20 **2.2 Patients with Renal Impairment**

21 In patients with stable renal function, creatinine clearance ( $C_{Cr}$ ) can be reasonably well  
22 estimated using the equation of Cockcroft and Gault:

23 For females  $C_{Cr}=(0.85)(140-\text{age})(\text{weight})/[(72)(S_{Cr})]$

24 For males  $C_{Cr}=(140-\text{age})(\text{weight})/[(72)(S_{Cr})]$

25 where age is in years, weight is in kilograms and  $S_{Cr}$  is serum creatinine in mg/dL.

26 The dose of GRALISE should be adjusted in patients with reduced renal function,  
27 according to Table 2. Patients with reduced renal function must initiate GRALISE at a daily dose  
28 of 300 mg. GRALISE should be titrated following the schedule outlined in Table 1. Daily  
29 dosing in patients with reduced renal function must be individualized based on tolerability and  
30 desired clinical benefit.

33

**Table 2: GRALISE Dosage Based on Renal Function**

Once-daily dosing	
Creatinine Clearance (mL/min)	GRALISE Dose (once daily with evening meal)
≥ 60	1800 mg
30 - 60	600 mg to 1800 mg
< 30	GRALISE should not be administered
patients receiving hemodialysis	GRALISE should not be administered

34

35 **3 DOSAGE FORMS AND STRENGTHS**

36       Tablets: 300 mg and 600 mg [*see Description (11) and How Supplied/Storage and*  
37 *Handling (16)*]

38 **4 CONTRAINDICATIONS**

39       GRALISE is contraindicated in patients with demonstrated hypersensitivity to the drug or  
40 its ingredients.

41 **5 WARNINGS AND PRECAUTIONS**

42       GRALISE is not interchangeable with other gabapentin products because of differing  
43 pharmacokinetic profiles that affect the frequency of administration.

44       The safety and effectiveness of GRALISE in patients with epilepsy has not been studied.

45 **5.1 Suicidal Behavior and Ideation**

46       Antiepileptic drugs (AEDs), including gabapentin, the active ingredient in GRALISE,  
47 increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication.  
48 Patients treated with any AED for any indication should be monitored for the emergence or  
49 worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or  
50 behavior.

51       Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of  
52 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice  
53 the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared  
54 to patients randomized to placebo. In these trials, which had a median treatment duration of 12  
55 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated  
56 patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an  
57 increase of approximately one case of suicidal thinking or behavior for every 530 patients treated.  
58 There were four suicides in drug-treated patients in the trials and none in placebo-treated patients,  
59 but the number is too small to allow any conclusion about drug effect on suicide.

60       The increased risk of suicidal thoughts or behavior with AEDs was observed as early as  
61 one week after starting drug treatment with AEDs and persisted for the duration of treatment  
62 assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk  
63 of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

64 The risk of suicidal thoughts or behavior was generally consistent among drugs in the data  
 65 analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a  
 66 range of indications suggests that the risk applies to all AEDs used for any indication. The risk  
 67 did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 3 shows  
 68 absolute and relative risk by indication for all evaluated AEDs.

69 **Table 3: Risk by Indication for Antiepileptic Drugs (including gabapentin, the**  
 70 **active ingredient in GRALISE) in the Pooled Analysis**

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

71  
 72 The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy  
 73 than in clinical trials for psychiatric or other conditions, but the absolute risk differences were  
 74 similar for the epilepsy and psychiatric indications.

75 Anyone considering prescribing GRALISE must balance the risk of suicidal thoughts or  
 76 behavior with the risk of untreated illness. Epilepsy and many other illnesses for which  
 77 products containing active components that are AEDs (such as gabapentin, the active  
 78 component in GRALISE) are prescribed are themselves associated with morbidity and  
 79 mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and  
 80 behavior emerge during treatment, the prescriber needs to consider whether the emergence of  
 81 these symptoms in any given patient may be related to the illness being treated.

82 Patients, their caregivers, and families should be informed that GRALISE contains  
 83 gabapentin which is also used to treat epilepsy and that AEDs increase the risk of suicidal  
 84 thoughts and behavior and should be advised of the need to be alert for the emergence or  
 85 worsening of the signs and symptoms of depression, any unusual changes in mood or behavior,  
 86 or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of  
 87 concern should be reported immediately to healthcare providers.

88 **5.2 Withdrawal of Gabapentin**

89 Gabapentin should be withdrawn gradually. If GRALISE is discontinued, this should be  
 90 done gradually over a minimum of 1 week or longer (at the discretion of the prescriber).

91 **5.3 Tumorigenic Potential**

92 In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high  
93 incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats.  
94 The clinical significance of this finding is unknown.

95 In clinical trials of gabapentin therapy in epilepsy comprising 2,085 patient-years of  
96 exposure in patients over 12 years of age, new tumors were reported in 10 patients, and pre-  
97 existing tumors worsened in 11 patients, during or within 2 years after discontinuing the drug.  
98 However, no similar patient population untreated with gabapentin was available to provide  
99 background tumor incidence and recurrence information for comparison. Therefore, the effect  
100 of gabapentin therapy on the incidence of new tumors in humans or on the worsening or  
101 recurrence of previously diagnosed tumors is unknown.

102 **5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan**  
103 **Hypersensitivity**

104 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as  
105 Multiorgan Hypersensitivity, has been reported in patients taking antiepileptic drugs, including  
106 GRALISE. Some of these events have been fatal or life-threatening. DRESS typically, although  
107 not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other  
108 organ system involvement, such as hepatitis, nephritis, hematological abnormalities,  
109 myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often  
110 present. Because this disorder is variable in its expression, other organ systems not noted here  
111 may be involved.

112 It is important to note that early manifestations of hypersensitivity, such as fever or  
113 lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms  
114 are present, the patient should be evaluated immediately. GRALISE should be discontinued if  
115 an alternative etiology for the signs or symptoms cannot be established.

116 **5.5 Laboratory Tests**

117 Clinical trial data do not indicate that routine monitoring of clinical laboratory procedures  
118 is necessary for the safe use of GRALISE. The value of monitoring gabapentin blood  
119 concentrations has not been established.

120 **6 ADVERSE REACTIONS**

121 **6.1 Clinical Trials Experience**

122 Because clinical trials are conducted under widely varying conditions, adverse reaction  
123 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical  
124 trials of another drug and may not reflect the rates observed in practice.

125 A total of 359 patients with neuropathic pain associated with postherpetic neuralgia have  
126 received GRALISE at doses up to 1800 mg daily during placebo-controlled clinical studies. In  
127 clinical trials in patients with postherpetic neuralgia, 9.7% of the 359 patients treated with

128 GRALISE and 6.9% of 364 patients treated with placebo discontinued prematurely due to  
129 adverse reactions. In the GRALISE treatment group, the most common reason for  
130 discontinuation due to adverse reactions was dizziness. Of GRALISE-treated patients who  
131 experienced adverse reactions in clinical studies, the majority of those adverse reactions were  
132 either "mild" or "moderate".

133 Table 4 lists all adverse reactions, regardless of causality, occurring in at least 1% of  
134 patients with neuropathic pain associated with postherpetic neuralgia in the GRALISE group for  
135 which the incidence was greater than in the placebo group.

136

137 **Table 4: Treatment-Emergent Adverse Reaction Incidence in Controlled Trials in**  
 138 **Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 1% of all**  
 139 **GRALISE-Treated Patients and More Frequent Than in the Placebo Group)**

<b>Body System – Preferred Term</b>	<b>GRALISE N = 359 %</b>	<b>Placebo N = 364 %</b>
<b>Ear and Labyrinth Disorders</b>		
Vertigo	1.4	0.5
<b>Gastrointestinal Disorders</b>		
Diarrhea	3.3	2.7
Dry mouth	2.8	1.4
Constipation	1.4	0.3
Dyspepsia	1.4	0.8
<b>General Disorders</b>		
Peripheral edema	3.9	0.3
Pain	1.1	0.5
<b>Infections and Infestations</b>		
Nasopharyngitis	2.5	2.2
Urinary tract infection	1.7	0.5
<b>Investigations</b>		
Weight increased	1.9	0.5
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Pain in extremity	1.9	0.5
Back pain	1.7	1.1
<b>Nervous System Disorders</b>		
Dizziness	10.9	2.2
Somnolence	4.5	2.7
Headache	4.2	4.1
Lethargy	1.1	0.3

140  
 141 In addition to the adverse reactions reported in Table 4 above, the following adverse  
 142 reactions with an uncertain relationship to GRALISE were reported during the clinical  
 143 development for the treatment of postherpetic neuralgia. Events in more than 1% of patients but  
 144 equally or more frequently in the GRALISE-treated patients than in the placebo group included  
 145 blood pressure increase, confusional state, gastroenteritis viral, herpes zoster, hypertension, joint  
 146 swelling, memory impairment, nausea, pneumonia, pyrexia, rash, seasonal allergy, and upper  
 147 respiratory infection.

148 **6.2 Postmarketing and Other Experience with other Formulations of Gabapentin**

149 In addition to the adverse experiences reported during clinical testing of gabapentin, the  
 150 following adverse experiences have been reported in patients receiving other formulations of

151 marketed gabapentin. These adverse experiences have not been listed above and data are  
152 insufficient to support an estimate of their incidence or to establish causation. The listing is  
153 alphabetized: angioedema, blood glucose fluctuation, breast enlargement, elevated creatine  
154 kinase, elevated liver function tests, erythema multiforme, fever, hyponatremia, jaundice,  
155 movement disorder, Stevens-Johnson syndrome.

156 Adverse events following the abrupt discontinuation of gabapentin immediate release have  
157 also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain  
158 and sweating.

## 159 **7 DRUG INTERACTIONS**

160 *In vitro* studies were conducted to investigate the potential of gabapentin to inhibit the  
161 major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6,  
162 CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective  
163 marker substrates and human liver microsomal preparations. Only at the highest concentration  
164 tested (171 mcg/mL; 1mM) was a slight degree of inhibition (14% to 30%) of isoform CYP2A6  
165 observed. No inhibition of any of the other isoforms tested was observed at gabapentin  
166 concentrations up to 171 mcg/mL (approximately 15 times the  $C_{max}$  at 3600 mg/day).

167 Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of  
168 commonly coadministered antiepileptic drugs.

169 The drug interaction data described in this section were obtained from studies involving  
170 healthy adults and adult patients with epilepsy.

### 171 **7.1 Phenytoin**

172 In a single (400 mg) and multiple dose (400 mg three times daily) study of gabapentin  
173 immediate release in epileptic patients (N=8) maintained on phenytoin monotherapy for at least 2  
174 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin  
175 and phenytoin had no effect on gabapentin pharmacokinetics.

### 176 **7.2 Carbamazepine**

177 Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide  
178 concentrations were not affected by concomitant gabapentin immediate release (400 mg three  
179 times daily; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by  
180 carbamazepine administration.

### 181 **7.3 Valproic Acid**

182 The mean steady-state trough serum valproic acid concentrations prior to and during  
183 concomitant gabapentin immediate release administration (400 mg three times daily; N=17)  
184 were not different and neither were gabapentin pharmacokinetic parameters affected by  
185 valproic acid.

186 **7.4 Phenobarbital**

187 Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin  
188 immediate release (300 mg three times daily; N=12) are identical whether the drugs are  
189 administered alone or together.

190 **7.5 Naproxen**

191 Coadministration of single doses of naproxen (250 mg) and gabapentin immediate release  
192 (125 mg) to 18 volunteers increased gabapentin absorption by 12% to 15%. Gabapentin  
193 immediate release had no effect on naproxen pharmacokinetics. The doses are lower than the  
194 therapeutic doses for both drugs. The effect of coadministration of these drugs at therapeutic  
195 doses is not known.

196 **7.6 Hydrocodone**

197 Coadministration of gabapentin immediate release (125 mg and 500 mg) and hydrocodone  
198 (10 mg) reduced hydrocodone  $C_{max}$  by 3% and 21%, respectively, and AUC by 4% and 22%,  
199 respectively. The mechanism of this interaction is unknown. Gabapentin AUC values were  
200 increased by 14%; the magnitude of the interaction at other doses is not known.

201 **7.7 Morphine**

202 When a single dose (60 mg) of controlled-release morphine capsule was administered 2  
203 hours prior to a single dose (600 mg) of gabapentin immediate release in 12 volunteers, mean  
204 gabapentin AUC values increased by 44% compared to gabapentin immediate release  
205 administered without morphine. The pharmacokinetics of morphine were not affected by  
206 administration of gabapentin immediate release 2 hours after morphine. The magnitude of this  
207 interaction at other doses is not known.

208 **7.8 Cimetidine**

209 Cimetidine 300 mg decreased the apparent oral clearance of gabapentin by 14% and  
210 creatinine clearance by 10%. The effect of gabapentin immediate release on cimetidine was not  
211 evaluated. This decrease is not expected to be clinically significant.

212 **7.9 Oral Contraceptives**

213 Gabapentin immediate release (400 mg three times daily) had no effect on the  
214 pharmacokinetics of norethindrone (2.5 mg) or ethinyl estradiol (50 mcg) administered as a  
215 single tablet, except that the  $C_{max}$  of norethindrone was increased by 13%. This interaction is  
216 not considered to be clinically significant.

217 **7.10 Antacid (containing aluminum hydroxide and magnesium hydroxide)**

218 An antacid containing aluminum hydroxide and magnesium hydroxide reduced the  
219 bioavailability of gabapentin immediate release by about approximately 20%, but by only 5%  
220 when gabapentin immediate release was taken 2 hours after the antacid. It is recommended that

221 GRALISE be taken at least 2 hours following the antacid (containing aluminum hydroxide and  
222 magnesium hydroxide) administration.

### 223 **7.11 Probenecid**

224 Gabapentin immediate release pharmacokinetic parameters were comparable with and  
225 without probenecid, indicating that gabapentin does not undergo renal tubular secretion by the  
226 pathway that is blocked by probenecid.

### 227 **7.12 Drug/Laboratory Test Interactions**

228 False positive readings were reported with the Ames-N-Multistix SG® dipstick test for  
229 urine protein when gabapentin was added to other antiepileptic drugs; therefore, the more  
230 specific sulfosalicylic acid precipitation procedure is recommended to determine the presence  
231 of urine protein.

## 232 **8 USE IN SPECIFIC POPULATIONS**

### 233 **8.1 Pregnancy**

234 Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing  
235 delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These  
236 effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the  
237 period of organogenesis, or approximately 3 to 8 times the maximum dose of 1800 mg/day given  
238 to PHN patients on a mg/m<sup>2</sup> basis. The no effect level was 500 mg/kg/day representing  
239 approximately the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> body surface area  
240 (BSA) basis. When rats were dosed prior to and during mating, and throughout gestation, pups  
241 from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent  
242 to approximately 3 to 11 times the MRHD on a mg/m<sup>2</sup> BSA basis. There was an increased  
243 incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general  
244 reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology  
245 study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study  
246 at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are  
247 approximately 3 to 11 times the maximum human dose of 1800 mg/day on a mg/m<sup>2</sup> basis; the no-  
248 effect doses were approximately 5 times (Fertility and General Reproductive Performance study)  
249 and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m<sup>2</sup> BSA  
250 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the  
251 incidence of malformations was not increased compared to controls in offspring of mice, rats, or  
252 rabbits given doses up to 100 times (mice), 60 times (rats), and 50 times (rabbits) the human  
253 daily dose on a mg/kg basis, or 8 times (mice), 10 times (rats), or 16 times (rabbits) the human  
254 daily dose on a mg/m<sup>2</sup> BSA basis. In a teratology study in rabbits, an increased incidence of  
255 postimplantation fetal loss occurred in dams exposed to 60, 300, and 1500 mg/kg/day, or 0.6 to  
256 16 times the maximum human dose on a mg/m<sup>2</sup> BSA basis. There are no adequate and well-  
257 controlled studies in pregnant women. This drug should be used during pregnancy only if the  
258 potential benefit justifies the potential risk to the fetus.

259 To provide information regarding the effects of *in utero* exposure to GRALISE,  
260 physicians are advised to recommend that pregnant patients taking GRALISE enroll in the  
261 North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by  
262 calling the toll free number 1-888-233-2334, and must be done by patients themselves.  
263 Information on the registry can also be found at the website  
264 <http://www.aedpregnancyregistry.org/>.

### 265 **8.3 Nursing Mothers**

266 Gabapentin is secreted into human milk following oral administration. A nursed infant  
267 could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the  
268 effect on the nursing infant is unknown, GRALISE should be used in women who are nursing  
269 only if the benefits clearly outweigh the risks.

### 270 **8.4 Pediatric Use**

271 The safety and effectiveness of GRALISE in the management of postherpetic neuralgia in  
272 patients less than 18 years of age has not been studied.

### 273 **8.5 Geriatric Use**

274 The total number of patients treated with GRALISE in controlled clinical trials in patients  
275 with postherpetic neuralgia was 359, of which 63% were 65 years of age or older. The types  
276 and incidence of adverse events were similar across age groups except for peripheral edema,  
277 which tended to increase in incidence with age.

278 GRALISE is known to be substantially excreted by the kidney. Reductions in GRALISE  
279 dose should be made in patients with age-related compromised renal function. [*see Dosage and*  
280 *Administration (2.2)*].

### 281 **8.6 Hepatic Impairment**

282 Because gabapentin is not metabolized, studies have not been conducted in patients with  
283 hepatic impairment.

### 284 **8.7 Renal Impairment**

285 GRALISE is known to be substantially excreted by the kidney. Dosage adjustment is  
286 necessary in patients with impaired renal function. GRALISE should not be administered in  
287 patients with CrCL between 15 and 30 or in patients undergoing hemodialysis. [*see Dosage and*  
288 *Administration (2.2)*].

## 289 **9 DRUG ABUSE AND DEPENDENCE**

290 The abuse and dependence potential of GRALISE has not been evaluated in human studies.

## 291 **10 OVERDOSAGE**

292 A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses  
293 as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing,  
294 ptosis, sedation, hypoactivity, or excitation.

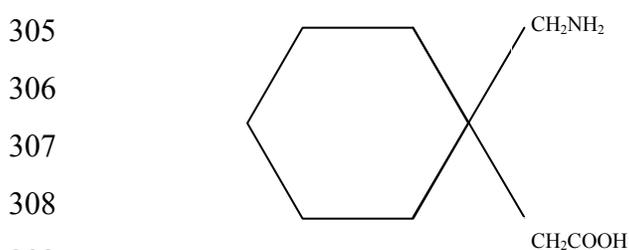
295 Acute oral overdoses of gabapentin immediate release in humans up to 49 grams have  
296 been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea  
297 were observed. All patients recovered with supportive care.

298 Gabapentin can be removed by hemodialysis. Although hemodialysis has not been  
299 performed in the few overdose cases reported, it may be indicated by the patient's clinical state  
300 or in patients with significant renal impairment.

## 301 11 DESCRIPTION

302 Gabapentin is 1-(aminomethyl)cyclohexaneacetic acid;  $\gamma$ -amino-2-cyclohexyl-butyric acid  
303 with a molecular formula of  $C_9H_{17}NO_2$  and a molecular weight of 171.24.

304 The structural formula is:



310  
311 Gabapentin is a white to off-white crystalline solid with a pKa1 of 3.7 and a pKa2 of 10.7.  
312 It is freely soluble in water and acidic and basic solutions. The log of the partition coefficient  
313 (n-octanol/ 0.05M phosphate buffer) at pH 7.4 is -1.25.

314 GRALISE is supplied as tablets containing 300 mg or 600 mg of gabapentin. GRALISE  
315 tablets swell in gastric fluid and gradually release gabapentin. Each 300 mg tablet contains the  
316 inactive ingredients copovidone, hypromellose, magnesium stearate, microcrystalline cellulose,  
317 polyethylene oxide, and Opadry<sup>®</sup> II white. Opadry<sup>®</sup> II white contains polyvinyl alcohol,  
318 titanium dioxide, talc, polyethylene glycol 3350, and lecithin (soya). Each 600 mg tablet  
319 contains the inactive ingredients copovidone, hypromellose, magnesium stearate, polyethylene  
320 oxide, and Opadry<sup>®</sup> II beige. Opadry<sup>®</sup> II beige contains polyvinyl alcohol, titanium dioxide, talc,  
321 polyethylene glycol 3350, iron oxide yellow, and iron oxide red.

## 322 12 CLINICAL PHARMACOLOGY

### 323 12.1 Mechanism of Action

324 The mechanism of action by which gabapentin exerts its analgesic action is unknown but in  
325 animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to  
326 a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli).  
327 Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and  
328 mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection  
329 model). Gabapentin also decreases pain-related responses after peripheral inflammation  
330 (carrageenan footpad test, late phase of formulin test), but does not alter immediate pain-related

331 behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to  
332 human pain is not known.

333 Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric  
334 acid), but it does not modify GABA<sub>A</sub> or GABA<sub>B</sub> radioligand binding, it is not converted  
335 metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or  
336 degradation. In radioligand binding assays at concentrations up to 100 μM, gabapentin did not  
337 exhibit affinity for a number of other receptor sites, including benzodiazepine, glutamate, N-  
338 methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-  
339 sensitive glycine; alpha 1, alpha 2, or beta adrenergic; adenosine A1 or A2; cholinergic,  
340 muscarinic, or nicotinic; dopamine D1 or D2; histamine H1; serotonin S1 or S2; opiate mu,  
341 delta, or kappa; cannabinoid 1; voltage-sensitive calcium channel sites labeled with nitrendipine  
342 or diltiazem; or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A20-  
343 alpha-benzoate. Gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or  
344 serotonin.

345 *In vitro* studies with radiolabeled gabapentin have revealed a gabapentin binding site in  
346 areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in  
347 animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium  
348 channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.  
349 It is hypothesized that gabapentin antagonizes thrombospondin binding to α2δ-1 as a receptor  
350 involved in excitatory synapse formation and suggested that gabapentin may function  
351 therapeutically by blocking new synapse formation.

## 352 **12.2 Pharmacodynamics**

353 No pharmacodynamic studies have been conducted with GRALISE.

## 354 **12.3 Pharmacokinetics**

### 355 ***Absorption and Bioavailability***

356 Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport  
357 system. Gabapentin bioavailability is not dose proportional; as the dose is increased,  
358 bioavailability decreases.

359 When GRALISE (1800 mg once daily) and gabapentin immediate release (600 mg three  
360 times a day) were administered with high fat meals (50% of calories from fat), GRALISE has a  
361 higher C<sub>max</sub> and lower AUC at steady state compared to gabapentin immediate release (Table 5).  
362 Time to reach maximum plasma concentration (T<sub>max</sub>) for GRALISE is 8 hours, which is about  
363 4-6 hours longer compared to gabapentin immediate release.

364

365 **Table 5: Mean (SD) Steady-State Pharmacokinetics for GRALISE and Gabapentin**  
 366 **Immediate Release in Plasma of Healthy Subjects (Day 5, n = 21)**

<b>Pharmacokinetic Parameters (Mean ± SD)</b>	<b>GRALISE 1800 mg QD</b>	<b>Gabapentin Immediate Release 600 mg TID</b>
<b>AUC<sub>0-24</sub></b> (ng • hr/mL)	132,808 ± 34,701	141,301 ± 29,759
<b>C<sub>max</sub></b> (ng/mL)	9,585 ± 2,326	8,536 ± 1,715
<b>C<sub>min</sub></b> (ng/mL)	1,842 ± 654	2,588 ± 783
<b>T<sub>max</sub> (hr) median (range)</b>	8 (3-12)	2 (1-5)*

\* = relative to most recent dose

367 Do not use GRALISE interchangeably with other gabapentin products because of differing  
 368 pharmacokinetic profiles that affect frequency of administration.

369  
 370 GRALISE should be taken with evening meals. If it is taken on an empty stomach, the  
 371 bioavailability will be substantially lower.

372  
 373 Administration of GRALISE with food increases the rate and extent of absorption of  
 374 gabapentin compared to the fasted state. C<sub>max</sub> of gabapentin increases 33-84% and AUC of  
 375 gabapentin increases 33-118% with food depending on the fat content of the meal. GRALISE  
 376 should be taken with food.

377 ***Distribution***

378 Gabapentin is less than 3% bound to plasma proteins. After 150 mg intravenous  
 379 administration, the mean ± SD volume of distribution is 58 ± 6 L.

380 ***Metabolism and Excretion***

381 Gabapentin is eliminated by renal excretion as unchanged drug. Gabapentin is not  
 382 appreciably metabolized in humans. In patients with normal renal function given gabapentin  
 383 immediate release 1200 to 3000 mg/day, the drug elimination half-life (t<sub>1/2</sub>) was 5 to 7 hours.  
 384 Elimination kinetics do not change with dose level or multiple doses.

385 Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly  
 386 proportional to creatinine clearance. In elderly patients and patients with impaired renal  
 387 function, plasma clearance is reduced. Gabapentin can be removed from plasma by  
 388 hemodialysis.

389 Dosage adjustment in patients with compromised renal function is necessary. In patients  
 390 undergoing hemodialysis, GRALISE should not be administered [*see Dosage and*  
 391 *Administration (2.2)*].

## 392 12.4 Special Populations

393 **Renal Insufficiency:** As renal function decreases, renal and plasma clearances and the  
394 apparent elimination rate constant decrease, while  $C_{\max}$  and  $t_{1/2}$  increase.

395 In patients (N=60) with creatinine clearance of at least 60, 30 to 59, or less than  
396 30 mL/min, the median renal clearance rates for a 400 mg single dose of gabapentin immediate  
397 release were 79, 36, and 11 mL/min, respectively, and the median  $t_{1/2}$  values were 9.2, 14, and  
398 40 hours, respectively.

399 Dosage adjustment is necessary in patients with impaired renal function [*see Dosage and*  
400 *Administration (2.2)*].

401 **Hemodialysis:** In a study in anuric adult subjects (N=11), the apparent elimination half-  
402 life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-  
403 life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on  
404 gabapentin elimination in anuric subjects. GRALISE should not be administered in patients  
405 undergoing hemodialysis. Alternative formulations of gabapentin products should be  
406 considered in patients undergoing hemodialysis.

407 **Elderly:** Apparent oral and renal clearances of gabapentin decrease with increasing age,  
408 although this may be related to the decline in renal function with age. Reductions in gabapentin  
409 dose should be made in patients with age-related compromised renal function [*see Dosage and*  
410 *Administration (2.2)*].

411 **Hepatic Impairment:** Because gabapentin is not metabolized, studies have not been  
412 conducted in patients with hepatic impairment.

413 **Pediatrics:** The pharmacokinetics of GRALISE have not been studied in patients less than  
414 18 years of age.

415 **Gender:** Although no formal study has been conducted to compare the pharmacokinetics  
416 of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and  
417 females are similar and there are no significant gender differences.

418 **Race:** Pharmacokinetic differences due to race have not been studied. Because gabapentin  
419 is primarily renally excreted and there are no important racial differences in creatinine clearance,  
420 pharmacokinetic differences due to race are not expected.

## 421 13 NONCLINICAL TOXICOLOGY

### 422 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

423 Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at  
424 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence  
425 of pancreatic acinar cell adenoma and carcinomas was found in male rats receiving the high  
426 dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma  
427 concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg/day were more than  
428 10 times higher than plasma concentrations in humans receiving 1800 mg per day and in rats

429 receiving 1000 mg/kg/day peak plasma concentrations were more than 6.5 times higher than in  
430 humans receiving 1800 mg/day. The pancreatic acinar cell carcinomas did not affect survival,  
431 did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic  
432 risk in humans is unclear.

433 Studies designed to investigate the mechanism of gabapentin-induced pancreatic  
434 carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar  
435 cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is  
436 not known whether gabapentin has the ability to increase cell proliferation in other cell types or  
437 in other species, including humans.

438 Gabapentin did not demonstrate mutagenic or genotoxic potential in 3 *in vitro* and 4 *in*  
439 *vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in  
440 Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations  
441 in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal  
442 aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was  
443 negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA  
444 synthesis in hepatocytes from rats given gabapentin.

445 No adverse effects on fertility or reproduction were observed in rats at doses up to  
446 2000 mg/kg (approximately 11 times the maximum recommended human dose on an mg/m<sup>2</sup>  
447 basis).

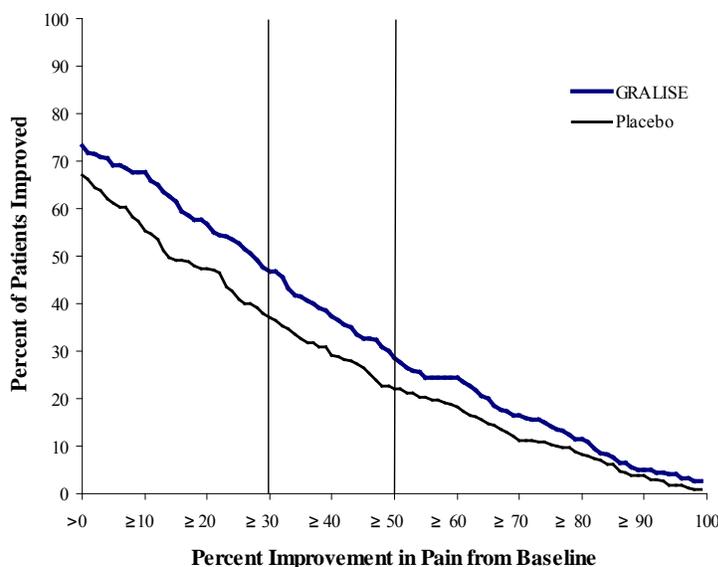
#### 448 **14 CLINICAL STUDIES**

449 The efficacy of GRALISE for the management of postherpetic neuralgia was established  
450 in a double-blind, placebo-controlled, multicenter study. This study enrolled patients between  
451 the age of 21 to 89 with postherpetic neuralgia persisting for at least 6 months following healing  
452 of herpes zoster rash and a minimum baseline pain intensity score of at least 4 on an 11-point  
453 numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain).

454 This 11-week study compared GRALISE 1800 mg once daily with placebo. A total of 221  
455 and 231 patients were treated with GRALISE or placebo, respectively. The study treatment  
456 including titration for all patients comprised a 10-week treatment period followed by 1-week of  
457 dose tapering. Double-blind treatment began with titration starting at 300 mg/day and titrated  
458 up to a total daily dose of 1800 mg over 2 weeks, followed by 8 weeks fixed dosing at 1800 mg  
459 once daily, and then 1 week of dose tapering. During the 8-week stable dosing period, patients  
460 took 3 active or placebo tablets each night with the evening meal. During baseline and  
461 treatment, patients recorded their pain in a daily diary using an 11-point numeric pain rating  
462 scale. The mean baseline pain score was 6.6 and 6.5 for GRALISE and placebo-treated patients,  
463 respectively.

464 Treatment with GRALISE statistically significantly improved the endpoint mean pain  
465 score from baseline. For various degrees of improvement in pain from baseline to study  
466 endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The  
467 figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also

468 included at every level of improvement below 50%. Patients who did not complete the study  
469 were assigned 0% improvement.



470

471 **Figure 1: Percent of Patients Achieving Various Levels of Pain Relief**

472 **16 HOW SUPPLIED/STORAGE AND HANDLING**

473 GRALISE (gabapentin) Tablets are supplied as follows:

474 **300 mg tablets:**

475 GRALISE 300 mg tablets are white, oval shaped tablets debossed with “SLV” on one side  
476 and “300” on the other side.

477 NDC 13913-004-13 (Bottle of 30)

478 NDC 13913-004-19 (Bottle of 90)

479 **600 mg tablets:**

480 GRALISE 600 mg tablets are beige, oval shaped tablets debossed with “SLV” on one side  
481 and “600” on the other side.

482 NDC 13913-005-19 (Bottle of 90)

483 **30-Day Starter Pack:**

484 NDC 13913-006-16 (Blister package containing 78 tablets: 9 x 300 mg tablets and 69 x  
485 600 mg tablets)

486 **Storage**

487 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP  
488 Controlled Room Temperature].

489 Keep out of reach of children.

490

## 491 **17 PATIENT COUNSELING INFORMATION**

492 • Advise patients that GRALISE is not interchangeable with other formulations of  
493 gabapentin.

494 • Advise patients to take GRALISE only as prescribed. GRALISE may cause dizziness,  
495 somnolence, and other signs and symptoms of CNS depression.

496 • Advise patients not to drive or operate other complex machinery until they have gained  
497 sufficient experience on GRALISE to gauge whether or not it adversely affects their  
498 mental and/or motor performance. Advise patients who require concomitant treatment  
499 with morphine to tell their prescriber if they develop signs of CNS depression such as  
500 somnolence. If this occurs the dose of GRALISE or morphine should be reduced  
501 accordingly.

502 • Advise patients that if they miss a dose of GRALISE to take it with food as soon as they  
503 remember. If it is almost time for the next dose, just skip the missed dose and take the  
504 next dose at the regular time. Do not take two doses at the same time.

505 • Advise patients that if they take too much GRALISE, to call their healthcare provider or  
506 poison control center, or go to the nearest emergency room right away.

### 507 **17.1 Medication Guide**

508 Advise patients of the availability of a Medication Guide, and instruct them to read the  
509 Medication Guide prior to taking GRALISE.

### 510 **17.2 Suicidal Thoughts and Behavior**

511 Advise patients, their caregivers, and families that AEDs, including gabapentin, the active  
512 ingredient in GRALISE, may increase the risk of suicidal thoughts and behavior and should be  
513 advised of the need to be alert for the emergence or worsening of symptoms of depression, any  
514 unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or  
515 thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare  
516 providers [*see Warnings and Precautions (5.1)*].

### 517 **17.3 Dosing and Administration**

518 Advise patients that GRALISE should be taken orally once-daily with the evening meal.  
519 GRALISE tablets should be swallowed whole. Do not split, crush, or chew the tablets [*see*  
520 *Dosage and Administration (2.1)*].

521

### 522 **Marketed by:**

523 Depomed, Inc.

524 Menlo Park, CA 94025

525

526 Opadry® is a registered trademark of BPSI Holdings, LLC.

527

528 © 2012 Depomed, Inc.

529 GRA-004-C.5 SEP 2012

530 Issued SEP 2012

531

532

533 U.S. Patents: 7,438,927; 6,340,475; 6,488,962; 6,635,280; 6,723,340; 7,731,989; 8,192,756; 8,252,332



534

535

536

537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569

**MEDICATION GUIDE**  
**GRALISE® (gra leez')**  
**(gabapentin) Tablets**

Read this Medication Guide before you start taking GRALISE and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about GRALISE, ask your healthcare provider or pharmacist.

**What is the most important information I should know about GRALISE?**

**Do not stop taking GRALISE without first talking with your healthcare provider.** Stopping GRALISE suddenly can cause serious problems.

Like other antiepileptic drugs, gabapentin, the active ingredient in GRALISE, may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. However, it is not known if GRALISE is safe and effective in people with seizure problems (epilepsy). Therefore, GRALISE should not be used in place of other gabapentin products.

**Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

**How can I watch for early symptoms of suicidal thoughts and actions?**

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

- 570 • Call your healthcare provider between visits as needed, especially if you are worried  
571 about symptoms.

572 **Do not stop taking GRALISE without first talking with your healthcare provider.**

- 573 • Stopping GRALISE suddenly can cause serious problems.

574 **What is GRALISE?**

575 GRALISE is a prescription medicine used in adults, 18 years and older, to treat:

- 576 • pain from damaged nerves (neuropathic pain) that follows healing of shingles (a painful  
577 rash that comes after a herpes zoster infection).

578 It is not known if GRALISE is safe and effective in people with seizure problems (epilepsy).

579 It is not known if GRALISE is safe and effective in children under 18 years of age with  
580 postherpetic pain.

581 GRALISE is not interchangeable with other gabapentin products.

582 **Who should not take GRALISE?**

583 Do not take GRALISE if you are allergic to gabapentin or any of the ingredients in GRALISE.  
584 See the end of this Medication Guide for a complete list of ingredients in GRALISE.

585 **What should I tell my healthcare provider before taking GRALISE?**

586 Before taking GRALISE, tell your healthcare provider if you:

- 587 • have or have had depression, mood problems or suicidal thoughts or behavior  
588 • have seizures  
589 • have kidney problems or get kidney dialysis  
590 • are pregnant or plan to become pregnant. It is not known if GRALISE can harm your  
591 unborn baby. Tell your healthcare provider right away if you become pregnant while  
592 taking GRALISE. You and your healthcare provider will decide if you should take  
593 GRALISE while you are pregnant.
- 594 ○ If you become pregnant while taking GRALISE, talk to your healthcare provider  
595 about registering with the North American Antiepileptic Drug (NAAED)  
596 Pregnancy Registry. The purpose of this registry is to collect information about  
597 the safety of antiepileptic drugs, including gabapentin, the active ingredient in  
598 GRALISE, during pregnancy. You can enroll in this registry by calling 1-888-  
599 233-2334.
- 600 • are breastfeeding or plan to breastfeed. GRALISE can pass into your breast milk. You  
601 and your healthcare provider should decide how you will feed your baby while you take  
602 GRALISE.

603 Tell your healthcare provider about all the medicines you take including prescription and non-  
604 prescription medicines, vitamins or herbal supplements.

605 Taking GRALISE with certain other medicines can cause side effects or affect how well they  
606 work. Do not start or stop other medicines without talking to your healthcare provider.

607 Know the medicines you take. Keep a list of them and show it to your healthcare provider and  
608 pharmacist when you get a new medicine.

### 609 **How should I take GRALISE?**

610 • Take GRALISE exactly as prescribed. Your healthcare provider will tell you how much  
611 GRALISE to take and when to take it. Take GRALISE at the same time each day.

612 • **Do not change your dose or stop taking GRALISE without talking with your**  
613 **healthcare provider.** If you stop taking GRALISE suddenly, you may experience side  
614 effects. Talk with your healthcare provider about how to stop GRALISE slowly.

615 • Take GRALISE with food one time each day with your evening meal.

616 • Take GRALISE tablets whole. Do not split, crush, or chew GRALISE tablets before  
617 swallowing.

618 • Your healthcare provider may change your dose of GRALISE. Do not change your dose  
619 of GRALISE without talking to your healthcare provider.

620 • If you miss a dose, take it as soon as you remember with food. If it is almost time for  
621 your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not**  
622 **take two doses at the same time.**

623 • If you take too much GRALISE, call your healthcare provider or poison control center,  
624 or go to the nearest emergency room right away.

625 • If you are taking an antacid containing aluminum hydroxide and magnesium hydroxide,  
626 it is recommended that GRALISE be taken at least 2 hours following administration of  
627 the antacid.

### 628 **What should I avoid while taking GRALISE?**

629 • Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking  
630 GRALISE without first talking to your healthcare provider. Taking GRALISE with  
631 alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or  
632 dizziness worse.

633 • Do not operate heavy machines or do other dangerous activities until you know how  
634 GRALISE affects you. GRALISE can slow your thinking and motor skills.

635 **What are the possible side effects of GRALISE?**

636 The most common side effect of GRALISE is:

- 637
  - dizziness

638 Tell your healthcare provider about any side effect that bothers you or that does not go away.

639 These are not all the possible side effects of GRALISE. For more information, ask your  
640 healthcare provider or pharmacist.

641 Call your doctor for medical advice about side effects. You may report side effects to FDA at  
642 1-800-FDA-1088.

643

644 **How should I store GRALISE?**

645 Store GRALISE at 59°F to 86°F (15°C to 30°C)

- 646
  - **Keep GRALISE and all medicines out of the reach of children.**

647 **General information about the safe and effective use of GRALISE**

648 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.  
649 Do not use GRALISE for a condition for which it was not prescribed. Do not give GRALISE to  
650 other people, even if they have the same symptoms you have. It may harm them.

651 This Medication Guide summarizes the most important information about GRALISE. If you  
652 would like more information, talk with your healthcare provider. You can ask your healthcare  
653 provider or pharmacist for information about GRALISE that is written for health professionals.

654 For more information about GRALISE, call 1-866-458-6389.

655 **What are the ingredients in GRALISE?**

656 Active ingredient: gabapentin

657 Inactive ingredients:

658 300 mg tablet: copovidone, hypromellose, magnesium stearate, microcrystalline cellulose,  
659 polyethylene oxide, and Opadry® II white. Opadry® II white contains polyvinyl alcohol,  
660 titanium dioxide, talc, polyethylene glycol 3350, and lecithin (soya).

661 600 mg tablet: copovidone, hypromellose, magnesium stearate, polyethylene oxide, and  
662 Opadry® II beige. Opadry® II beige contains polyvinyl alcohol, titanium dioxide, talc,  
663 polyethylene glycol 3350, iron oxide yellow, and iron oxide red.

664

665 **Marketed by:**

666 Depomed, Inc.

667 Menlo Park, CA 94025

668

669 Opadry® is a registered trademark of BPSI Holdings, LLC.

670

671 © 2012 Depomed, Inc.

672 GRA-004-C.5 SEP 2012

673 Issued SEP 2012

674 This Medication Guide has been approved by the U.S. Food and Drug Administration.

675

676

